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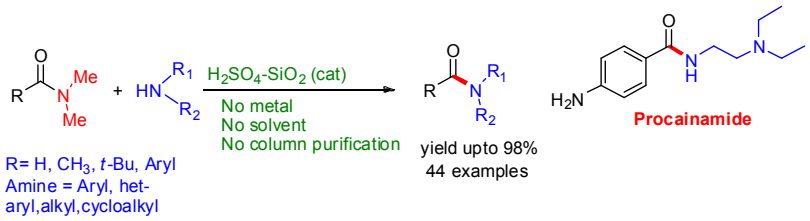
Graphical Abstract

Sulphuric acid immobilized on silica gel (H_2SO_4-SiO_2) as an eco-friendly catalyst for transamidation

Sk. Rasheed, D. Nageswar Rao, A. Siva Reddy, Ravi Shankar and Parthasarathi Das*



A novel method of transamidation of carboxamides with amines using catalytic amounts of H_2SO_4-SiO_2 under solvent-free conditions has been developed. The scope of the methodology has been demonstrated with aromatic/heteroaromatic, cyclic/acyclic, primary, and secondary amines. Versatility of this methodology has further been demonstrated by the synthesis of commercially available drug procainamide.

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Sulphuric acid immobilized on silica gel (H_2SO_4-SiO_2) as an eco-friendly catalyst for transamidation

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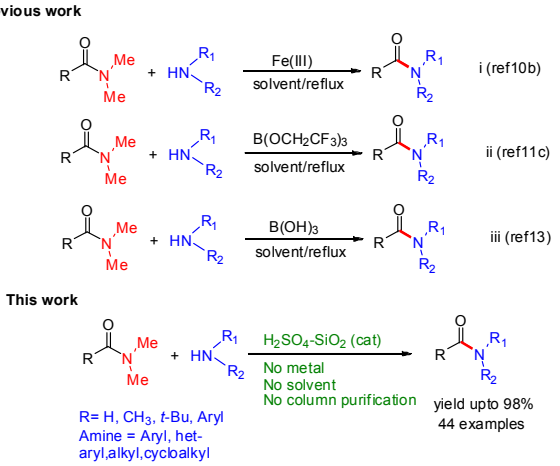
A novel method of transamidation of carboxamides with amines by using catalytic amount of H_2SO_4-SiO_2 has been developed under solvent free conditions. The transamidation is compatible with wide range of aromatic, heteroaromatic, aliphatic, cyclic/ acyclic primary or secondary amines. The metal/ solvent-free conditions represent a significant improvement over other existing methods as it can be performed in open air conditions and no column purification is required. The versatility of this methodology was further demonstrated by synthesizing commercially available drug procainamide.

Introduction

The amide bond is widely present both in natural products and synthetic compounds. Presence of amide functionality in top selling pharmaceutical products, makes the amidation reaction one of the most commonly used reactions in medicinal chemistry.[1,2] Traditionally, amides have been synthesized by the reactions of carboxylic acids[3] and their derivatives[4] with amines, which in general suffers from harsh reaction conditions and large amount of by-products, thus severely impedes the large scale production. Therefore, atom-economical synthesis of amides without use of hazardous reagents or without generating waste is a formidable challenge in organic synthesis. The transamidation process has emerged as an alternative and attractive protocol for amide bond formation.[5] Recently, elegant examples of transamidation reaction from the groups of Stahl,[6] Williams,[7] Myers,[8] Beller[9] and other groups have been reported.[10] Despite their wide scope these reactions suffer from high temperature and required transition-metal catalyst to promote the transamidation. Boron-mediated transamidation has been reported in the literature,[11] where the boron reagents has been used either in stoichiometric or in catalytic amounts. Metal-free methods utilizing catalytic hydroxylamine hydrochloride[12], L-proline[13] and ammonium chloride[14] have also been reported. But these catalysts are active only in organic solvents except few are reported under solvent-free conditions.[10d,13] Moreover, the scope of these methods are only limited to primary amides and most cases to primary amines. Clearly there is a lack of an efficient, general and environmentally benign protocol for transamidation.

In the recent years, H_2SO_4-SiO_2 has shown great potentiality as an efficient and easily retrievable solid catalyst in promoting various important organic reactions under solvent-free conditions.[15] The high catalytic activity, the operational simplicity and the recyclability of H_2SO_4-SiO_2 make this reagent attractive for industrial use.[16] To the best of our knowledge, H_2SO_4-SiO_2 catalyzed transamidations have not been reported yet. Considering the economic attractiveness and environmental friendliness of H_2SO_4-SiO_2 as catalyst, we became interested in developing a general transamidation methodology of carboxamides with amines. Herein, we report our results for the first time (Scheme 1).



Scheme 1 Methods for transamidation

Results and discussion

Our initial studies focused on developing an efficient catalytic system for transamidation and we used *N*, *N*-dimethylbenzamide

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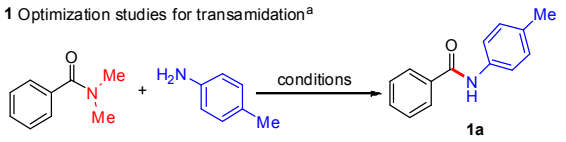
Journal Name

with *p*-toluidine as model system (Table 1). At first the reaction was performed in presence of silica (SiO_2) without solvent unfortunately no transamidation happened even at 100 ^oC (entry 1, Table 1). But to our delight use of H_2SO_4-SiO_2 (100 mol %) at 100 ^oC gave transamidation product **1a** in 50 % yield. Temperature variation revealed that SiO_2-H_2SO_4 works more efficiently at 70 ^oC (entry 3, Table 1). At room temperature (entry 4, Table 1) the reaction was not moving even after 12 h where as at 50 ^{o} C lower yield (50%) was obtained (entry 5, Table 1). Encouraged with this results, we performed the reaction by using 20 mol% H_2SO_4-SiO_2 at 70 ^oC (entry 6, Table 1) and the transamidation product was isolated in 63% yield. The yield of product was further increased (70%) when the catalyst loading decreased to 10 mol% (entry 7, Table 1). The optimum condition was obtained when we performed the reaction by using 5 mol% H_2SO_4-SiO_2 at 70 ^oC and the isolated yield was 90 % (entry 8, Table 1). Interestingly, when the reaction temperature was increased to 100 ^oC (entry 9, Table 1) yield was decreased due to hydrolysis of corresponding amide. The catalytic potential of other protic acid on silica (TfOH-SiO_2; AcOH-SiO_2; $HClO_4$-SiO_2) was also assessed found are less effective (entries 10-12, Table 1). When we used only H_2SO_4 (5 mol%) the yield was decreased to 73% (Table 1, entry 13).

Table 1 Optimization studies for transamidation[a]

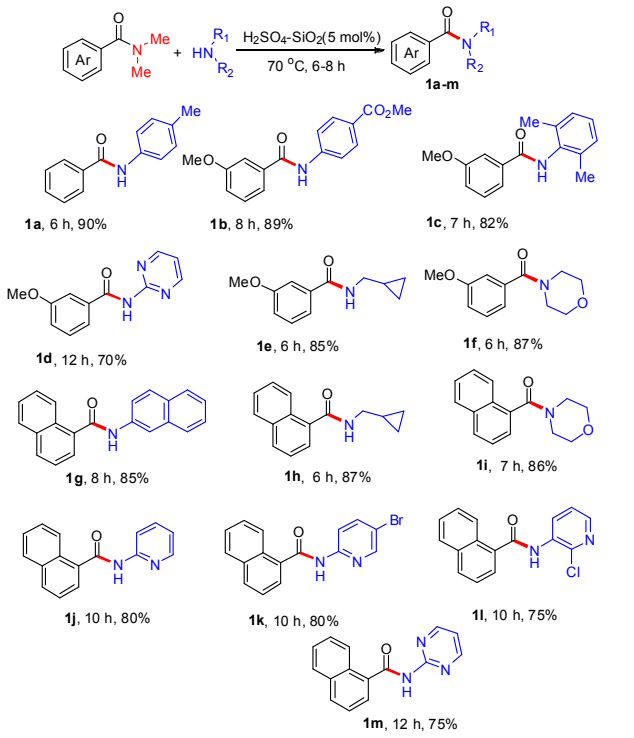


Entry	Catalyst(mol%)	Temp [^oC]	Time (h)	Yield(%)[b]
1	SiO_2 (100)	100	12	n.r
2	H_2SO_4-SiO_2 (100)	100	6	50
3	H_2SO_4-SiO_2 (100)	70	6	60
4	H_2SO_4-SiO_2 (100)	rt	12	n.r.
5	H_2SO_4-SiO_2 (100)	50	12	50
6	H_2SO_4-SiO_2 (20)	70	12	63
7	H_2SO_4-SiO_2 (10)	70	12	70
8	H_2SO_4-SiO_2 **(5)**	**70**	**6**	**90**
9	H_2SO_4-SiO_2 (5)	100	6	75
10	TfOH-SiO_2 (100)	100	12	45
11	AcOH-SiO_2 (100)	100	3	25
12	$HClO_4$-SiO_2 (100)	100	6	40
13	H_2SO_4 (5)	70	6	73

[a]Reaction conditions: amine (0.93 mmol), *N*, N-dimethyl benzamide (2.8 mmol) H_2SO_4-SiO_2 (5 mol%), temp = 70 ^oC, air; b = isolated yield; n.r.= no reaction.

With the optimized catalytic conditions in hand at first the scope of the amidation reactions were explored with a wide range of amines and various *N*, *N*-dimethyl benzamides results are summarized in Table 2. *N*-aryl/heteroaryl benzamides are the important structural core of many FDA approved drugs.[17] Thus, finding a general route for this kind of amide bond formation will definitely add value to drug discovery process. In general, the transamidation of *N*, *N*-dimethyl benzamide with aryl/heteroaryl amines (electron-neutral, -rich, -deficient), aliphatic and cyclic secondary amines gave corresponding transamidation products in very good yields (70-90%) (**1a-f**). Interestingly, sterically hindered arylamines like 2,6 dimethyl aniline undergoes the reaction smoothly and the resulted amide (**1c**) isolated in good yield (82%). Less reactive heteroaromatic like 2-aminopyrimidine gave the transamidation product (**1d**), albeit in low yield (70%) and in larger reaction time. To enhance the further substrate scope *N*,*N*-dimethyl napthamides were subjected for transamidation raction with various amines. To our delight aromatic/heteroaromatic/aliphatic amines undergoes smooth transamidation (**1g-m**) with excellent yields (75-87%). It is noteworthy to mention that functional groups like bromo (**1k**) or chloro (**1l**) are tolerable under these reaction conditions.

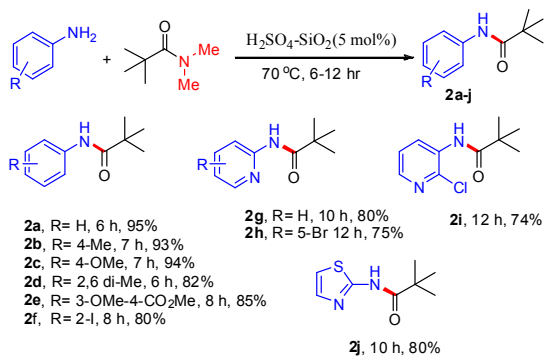
Table 2 Synthesis of benzamides/napthamide *via* transamidation[a]



[a]Reaction conditions: amine (0.93 mmol.), *N*,*N*- dimethyl benzamide (2.8 mmol), H_2SO_4-SiO_2 (5 mol%), 70 ^oC, air.

N-aryl/heteroaryl pivalamides are important in organic synthesis as they works as directing group in many transition-metal catalyzed reactions.[18] Further *N*-aryl pivalamides also found in many medicinally important compounds.[19]

Table 3 Synthesis of *N*-aryl/hetaryl pivalamide *via* transamidation[a]



[a]Reaction conditions: amine (0.93 mmol), *N*,*N*-dimethylpivalamide (2.8 mmol), H_2SO_4-SiO_2 (5 mol%), 70 ^oC, air

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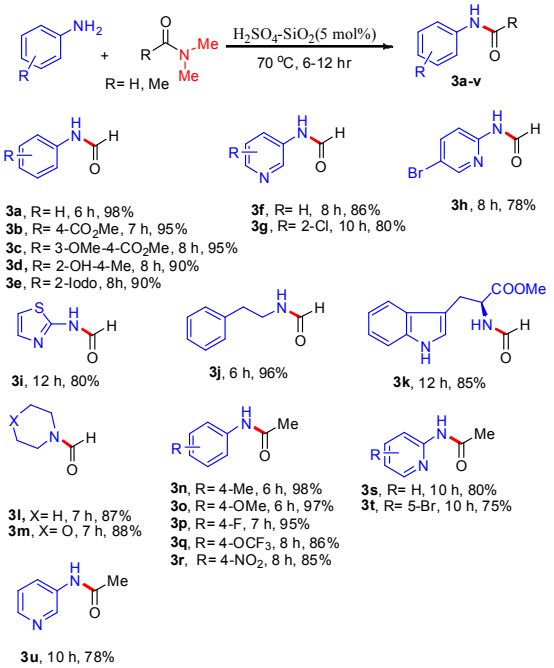
Thus, finding general synthetic protocol for this kind of amide bond formation will be interesting in organic synthesis. Here, we have applied this optimized transamidation conditions in synthesis of various *N*-aryl/heteroaryl pivalamides (Table 3). The versatility of this reaction was demonstrated with different aryl amines undergoes transamidation reaction with *N*, *N*-dimethyl pivalamide to give the corresponding *N*-aryl pivalamides (**2a-f**) in excellent yields (80-95%). Under these conditions heteroaromatic amines also been tested and the resulted *N*-heteroaryl pivalamides are isolated (**2g-j**) in good yields (74-80%).

Typically, the *N*-acetylation and *N*-formylation of an amine is carried out using hazardous, toxic, and unstable reagents.[20] This led us to carry out a more comprehensive study of scope and limitation of acetylation/formylation using the present methodology. As shown in Table 4 the aromatic/heteroaromatic amines bearing either electron-rich or electron-deficient substituent in the aromatic ring all underwent the reactions smoothly to give the desired *N*-aryl formamides (**3a-i**) in excellent yields (78-98%). Functional groups like -CO_2Me (**3b-c**), hydroxyl (**3d**) and iodo (**3e**) are tolerable under this optimized conditions. In this context, we performed the formylation of methyl ester of L-tryptophan and the corresponding formylated product (**3k**) was obtained in good yield (85%).

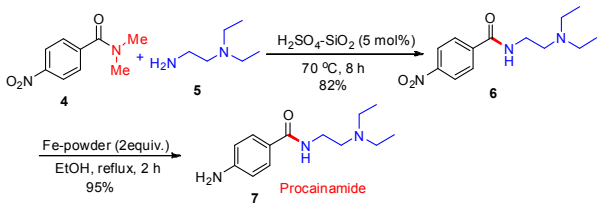
Table 4 Acetylation and formylation of amines *via* transamidation[a]



[a]Reaction conditions: amine (1.05 mmol), DMF/DMA(3.22 mmol & 3.12 mmol), H_2SO_4-SiO_2 (5 mol%), 70 °C, air.

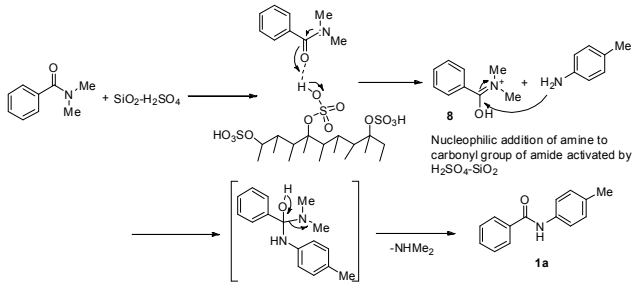
Finally, under these optimized conditions the transamidation of *N*, *N*-dimethyacetamide with various amines was examined. The results presented in Table 4 revealed that both the aryl and hereto aryl amines underwent smooth transamidation to give the desired products (**3n-u**) in high yields (75-98%). It is important to highlight that this result represents a useful method for the protection of primary amines with excellent functional group tolerability.

Procainamide[21] an antiarrhythmic drug used for treatment of cardiac arrhythmias prepared by following these optimized transamidation protocol (Scheme 2). In this synthesis nitro benzamide derivative (**4**) under goes smooth transamidation with diamine (**5**) to give benzamide **6** in very good yield (82%). Subsequent reduction of nitro group gave the desired procainamide (**7**).



Scheme 2 Synthesis of Procainamide

Based on the results and the fact that H_2SO_4-SiO_2 plays the role of transferring protons from its solid surface.[15b] A plausible mechanism for the transamidation has been presented in Scheme 3. The protonation and activation of the amide bond of *N*, *N*-dimethyl benzamide by sulfonic group of H_2SO_4-SiO_2 generates the cationic intermediate **8**. Now, the cationic intermediate reacts with amine nuclophiles, which on further elimination of -$NHMe_2$ provides the transamidation product **1a**.



Scheme 3 Plausible transamidatiom mechanism

Conclusion

We have developed an environment friendly H_2SO_4-SiO_2 catalytic system for transamidation. Presented catalytic system explored with substituted aromatic, heteroaromatic, and aliphatic/alicyclic primary amines, as well as secondary amines with carboxamides. The scope of H_2SO_4-SiO_2 catalytic system was also examined further for acetylation and formylation. Due to its manipulation ease, low-cost, and benign character, the H_2SO_4-SiO_2 catalytic system described here represents an excellent complement to the previously reported protocols. This methodology is general and definitely will add value into the fastest growing area of transamidation chemistry.

Experimental Section

General Information

Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel plates (60 F254; MERCK). TLC plates were visualized by exposing UV light or by iodine vapors or immersion in ninhydrin followed by heating on hot plate. ^{1}H and ^{13}C NMR spectra were recorded with BRUKER

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Journal Name

500 and 400 MHz NMR instruments. Mass spectra were recorded with VARIAN GC-MS instrument. HRMS spectra were recorded with LCMS-QTOF Module No. G6540 A (UHD) instrument. IR spectra were recorded on Jasco FT/ IR-5300 spectrophotometer. Melting points were measured in open capillary tubes and are uncorrected. Unless otherwise indicated, chemicals and solvents were purchased from commercial suppliers.

Preparation of Sulphuric acid adsorbed on silica gel (SiO_2-H_2SO_4):

The preparation of H_2SO_4-SiO_2 was carried out by following reported procedure.[15a] To a suspension of silica gel (29.5 g, 230–400 mesh size) in EtOAc (60 mL) was added H_2SO_4 (1.5 g, 15.5 mmol, 0.8 mL of a 98% aq. solution of H_2SO_4) and the mixture was stirred magnetically for 30 min at rt. The EtOAc was removed under reduced pressure (rotary evaporator) and the residue was heated at 100 °C for 72 h under vacuum to afford H_2SO_4-SiO_2 as a free flowing powder.

General Procedure:

To a mixture of aniline (0.93 mmol) and *N*, *N*-dimethyl amide (2.8 mmol) H_2SO_4-SiO_2 (5 mol%) was added. The mixture was stirred at 70 °C and progress of the reaction monitored by TLC. After completion of the reaction, the mixture was diluted with EtOAc (20 ml), filtered, water (30 ml) added, the solution extracted with EtOAc (3 x 15 ml), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was subjected to column chromatography to obtain the pure desired product.

***N*-(*p*-tolyl)benzamide (1a):**[22a] Colourless solid (90%); mp. 133-135 °C ; IR (NaCl) ν(cm^{-1}) 3339, 2923, 1650, 1597, 1579, 1514, 1404, 1320, 1121, 1018, 926, 813, 772, 713; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.5 Hz, 2H), 7.77 (s, 1H), 7.52 (m, 5H), 7.18 (d, *J* = 8.2 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 135.3, 135.0, 134.2, 131.7, 129.6, 128.78, 127.0, 120.2, 20.9; HRMS (ESI): m/z Calcd. for $C_{14}H_{14}NO$ $[M+H]^+$: 212.1070; found: 212.1073.

Methyl 4-(3-methoxybenzamido)benzoate (1b):[22b] Colourless solid (89%); mp. 112-114 °C; IR (NaCl) ν(cm^{-1}) 3440, 2923, 1682, 1609, 1585, 1491, 1457, 1439, 1308, 1282, 1236, 1194, 1103, 1049, 1018, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (t, *J* = 8.5 Hz, 2H), 7.64 (dd, *J* = 11.8, 2.9, 2H), 7.43 (t, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.19 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 159.8 , 159.5, 130.0, 129.8, 129.5, 122.9, 122.6, 121.1, 120.4, 114.8, 114.3, 55.5, 55.4; HRMS (ESI): m/z Calcd. for $C_{16}H_{16}NO_4$ $[M+H]^+$: 286.1074; found: 286.1079.

2,6-Dimethyl-*N*-phenylbenzamide (1c): Colourless solid (82%); mp. 149–152 °C ; IR (NaCl) ν(cm^{-1}) 3261, 2913, 2835, 1644, 1585, 1513, 1485, 1470, 1446, 1376, 1328, 1302, 1242, 1182, 1040, 993, 877, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 2.0 Hz,1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.42 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.13 (m, 3H), 3.88 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 159.9, 135.9, 135.6, 133.8, 129.7, 128.2, 127.4, 118.9, 117.9, 112.6, 55.5, 18.4; HRMS (ESI): m/z Calcd. for $C_{16}H_{18}NO_2$ $[M+H]^+$: 256.1332; found: 256.1336.

3-Methoxy-*N*-(pyrimidin-2-yl)benzamide (1d): Colourless solid (70%); mp. 110-112 °C; IR (NaCl) ν(cm^{-1}) 3436, 2924, 2853, 1694, 1599, 1583, 1567, 1487, 1452, 1430, 1408, 1290, 1265, 1212, 1180, 1123, 1083, 1041, 995, 801, 768; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 6.1 Hz, 1H), 7.24 (td, *J* = 8.1, 1.2 Hz, 2H), 7.13 (t, *J* = 5.4 Hz, 1H), 7.02 (dd, *J* = 8.2, 2.0 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 160.6, 159.7, 158.8, 135.5, 129.6, 121.6, 119.5, 118.8, 113.8, 55.4; HRMS (ESI): m/z Calcd. for $C_{12}H_{12}N_3O_2$ $[M+H]^+$: 230.0924; found: 230.0918.

***N*-(Cyclopropylmethyl)-3-methoxybenzamide (1e):** Colourless solid (85%); mp. 60-62 °C; IR (NaCl) ν(cm^{-1}) 3321, 2921, 2851, 1637, 1601, 1582, 1540, 1485, 1464, 1430, 1340, 1300, 1242, 1125, 1045, 1018, 876, 804; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.04 (dd, *J* = 7.9, 2.5 Hz, 1H), 6.22 (s, 1H), 3.86 (s, 3H), 3.31 (dd, *J* = 7.1, 5.5 Hz, 2H), 1.06 (m, 1H), 0.56 (q, *J* = 4.4 Hz, 2H), 0.28 (q, *J* = 4.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 159.8, 136.2, 129.5, 118.6, 117.5, 112.3, 55.4, 44.9, 10.7, 3.5; HRMS (ESI): m/z Calcd. for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1176; found: 206.1195.

(3-Methoxyphenyl)(morpholino)methanone (1f):[22c] Yellow oil (87%); IR (NaCl) ν(cm^{-1}) 3257, 2964, 2919, 2854, 1643, 1580, 1577, 1488, 1454, 1363, 1288, 1185, 1141, 1114, 1070, 1044, 1022, 995, 946, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 1H), 6.95 (d, *J* = 7.4 Hz, 3H), 3.82 (s, 3H), 3.77 (d, *J* = 3.0 Hz, 4H), 3.45 (d, *J* = 76.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 159.6, 136.5, 129.6, 119.0, 115.6, 112.4, 66.8, 55.3, 48.1; HRMS (ESI): m/z Calcd. for $C_{12}H_{16}NO_3$ $[M+H]^+$: 222.1125; found: 222.1122.

***N*-(Naphthalen-2-yl)-1-naphthamide (1g):** Colourless solid (85%); mp. 198-200 °C; IR (NaCl) ν(cm^{-1}) 3224, 2923, 1651, 1583, 1548, 1470, 1429, 1356, 1292, 1258, 1221, 898, 781; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 9.0 Hz, 2H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 7.3 Hz, 1H), 7.87 (m, 3H), 7.81 (d, *J* = 7.4 Hz, 1H), 7.60 (m, 4H), 7.52 (m, 1H), 7.45 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 135.4, 133.8, 133.7, 131.1, 130.8, 130.0, 128.9, 128.4, 127.7, 127.6, 127.4, 126.6, 125.2, 125.2, 125.1, 124.7, 119.7, 116.7; HRMS (ESI): m/z Calcd. for $C_{21}H_{16}NO$ $[M+H]^+$: 298.1227; found: 298.1227.

***N*-(Cyclopropylmethyl)-1-naphthamide (1h):** Colourless solid (87%); mp. 123-124 °C; IR (NaCl) ν(cm^{-1}) 3299, 2923, 2851, 1635, 1620, 1592, 1578, 1539, 1428, 1385, 1338, 1300, 1268, 1207, 1163, 1018, 806, 778; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.0 Hz, 1H), 7.88 (m, 2H), 7.62 (d, *J* = 7.0 Hz, 1H), 7.54 (m, 2H), 7.46 (t, *J* = 7.6 Hz, 1H), 6.12 (s, 1H), 3.41 (t, *J* = 8.2 Hz, 2H), 1.10 (m, 1H), 0.57 (q, *J* = 4.9 Hz 2H), 0.31 (q, *J* = 4.8 Hz,

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2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 134.7, 133.6, 130.4, 130.1, 128.3, 127.0, 126.4, 125.4, 124.8, 124.7, 44.8, 10.8, 3.5; HRMS (ESI): m/z Calcd. for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1227; found: 226.1231.

Naphthalen-1-yl(piperidin-1-yl)methanone (1i):[22c] Yellow color gel (86%); IR (NaCl) ν(cm^{-1}) 3055, 2918, 2854, 1634, 1592, 1508, 1466, 1432, 1361, 1300, 1281, 1267, 1249, 1154, 1114, 1067, 1044, 1018, 994, 847, 799, 780; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (t, *J* = 6.9 Hz, 3H), 7.51 (dd, *J* = 11.3, 4.2 Hz, 2H), 7.47 (dd, *J* = 8.1, 4.8 Hz, 1H), 7.41 (d, *J* = 6.9 Hz, 1H), 3.82 (t, *J* = 8.5 Hz, 4H), 3.49 (t, *J* = 8.7 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 133.6, 133.4, 129.5, 129.3, 128.5, 127.1, 126.5, 125.2, 124.6, 123.9, 66.9, 47.5; HRMS (ESI): m/z Calcd. for $C_{15}H_{16}NO_2$ $[M+H]^+$: 242.1176; found: 242.1176.

***N*-(Pyridin-2-yl)-1-naphthamide (1j):** [22d] Colourless solid (80%); mp. 103-105 °C; IR (NaCl) ν(cm^{-1}) 3438, 2924, 1680, 1609, 1580, 1488, 1455, 1432, 1422, 1318, 1292, 1226, 1184, 1113, 1041, 1028, 928, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.41 (d, *J* = 6.9 Hz, 1H), 8.32 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.67 (dd, *J* = 16.6, 7.5 Hz, 2H), 7.48 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 6.86 (t, *J* = 8.1 Hz, 1H); HRMS (ESI): m/z Calcd. for $C_{16}H_{13}N_2O$ $[M+H]^+$: 249.1023; found: 249.1018.

***N*-(4-Bromopyridin-2-yl)-1-naphthamide (1k):** Colourless solid (80%); mp. 164-165 °C ; IR (NaCl) ν(cm^{-1}) 3439, 2924, 1706, 1673, 1592, 1574, 1509, 1459, 1396, 1367, 1345, 1320, 1293, 1271, 1233, 1193, 1123, 1092, 783; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.94 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.75 (d, *J* = 7.1 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.42 (m, 3H), 7.10 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 151.9, 150.8, 141.0, 133.2, 133.1, 131.7, 129.9, 128.1, 127.5, 127.2, 126.5, 124.9, 124.0, 123.8, 119.5; HRMS (ESI): m/z Calcd. for $C_{16}H_{12}BrN_2O$ $[M+H]^+$: 327.0128; found: 327.0127.

***N*-(2-Chloropyridin-3-yl)-1-naphthamide (1l):** Colourless solid (75%); mp. 139-141 °C; IR (NaCl) ν(cm^{-1}) 3408, 2926, 2854, 1678, 1615, 1580, 1510, 1453, 1400, 1383, 1297, 1245, 1194, 1137, 1080, 1053, 1019, 869, 779; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.34 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 6.7 Hz, 1H), 7.71 (m, 2H), 7.45 (m, 3H), 6.90 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 146.0, 143.8, 134.7, 133.4, 133.3, 132.0, 131.1, 129.3, 128.4, 128.0, 127.4, 126.8, 126.2, 125.8, 124.2; HRMS (ESI): m/z Calcd. for $C1_6H_{12}ClN_2O$ $[M+H]^+$: 283.0633; found: 283.0639.

***N*-(Pyrimidin-2-yl)-1-naphthamide (1m):** Colourless oil (75%); IR (NaCl) ν(cm^{-1}) 3323, 2931, 1703, 1631, 1591, 1509, 1476, 1460, 1434, 1381, 1364, 1237, 1216, 1172, 1127, 1098, 1017, 863, 801, 781, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 8.6 Hz, 1H), 8.29 (d, *J* = 7.2 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.85 (dd, *J* = 8.8, 3.4 Hz, 2H), 7.60 (d, *J* = 7.3 Hz, 1H), 7.50 (m, 3H), 7.41 (dd, *J* = 7.0, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 135.0, 133.9, 133.4, 129.6, 128.8, 128.3, 127.8, 126.9, 126.3, 125.1, 124.7, 124.5, 123.2; HRMS (ESI): m/z Calcd. for $C_{15}H_{12}N_3O$ $[M+H]^+$: 250.0975; found:250.0969.

***N*-Phenylpivalamide (2a):**[23a] Colourless solid (95%); mp. 134-136 °C; IR (NaCl) ν(cm^{-1}) 3435, 2921, 2851, 1653, 1613, 1598, 1460, 1431, 1018, 745, 669 566; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 138.0, 128.9, 124.2, 119.9, 39.6, 27.6. HRMS (ESI): m/z Calcd. for $C_{11}H_{16}NO$ $[M+H]^+$: 178.1227; found: 178.1227.

***N*-(*p*-Tolyl)pivalamide (2b):**[23a] Colourless solid (93%); mp. 116-118 °C; IR (NaCl) ν(cm^{-1}) 3429, 2921, 2849, 1644, 1583, 1515, 1484, 1467, 1303, 1240, 1157, 1112, 1019, 769, 753, 721; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 2.31 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 135.4, 133.7, 129.4, 120.0, 39.5, 27.6, 20.8. HRMS (ESI): m/z Calcd. for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1383; found: 192.1387.

***N*-(4-Methoxyphenyl)pivalamide (2c):** [23a] Colourless solid (94%); mp. 115-116 °C; IR (NaCl) ν(cm^{-1}) 3441, 2921, 2851, 1670, 1619, 1594, 1544, 1404, 1237, 1018, 779, 669; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.9 Hz, 2H), 7.27 (s, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 156.3, 131.1, 121.9, 114.0, 55.5, 39.4, 27.6. HRMS (ESI): m/z Calcd. for $C_{12}H_{18}NO_2$ $[M+H]^+$: 208.1332; found: 208.1328.

***N*-(2,6-Dimethylphenyl)pivalamide (2d)**: [23b] Colourless solid (82%); mp. 203-204 °C; IR (NaCl) ν(cm^{-1}) 3271, 2928, 2871, 1650, 1592, 1514, 1478, 1439, 1400, 1367, 1297, 1222, 1177, 1091, 1036, 937, 913, 809, 764, 722; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (m, 3H), 6.89 (s, 1H), 2.20 (s, 6H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 135.4, 133.9, 128.1, 127.1, 39.2, 27.8, 18.2. HRMS (ESI): m/z Calcd. for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1540; found: 206.1546.

Methyl 2-methoxy-4-pivalamidobenzoate (2e): Colourless solid (85%); mp. 128-129 °C; IR (NaCl) ν(cm^{-1}) 3358, 2958, 287, 1707, 1672, 1608, 1590, 1523, 1479, 1451, 1434, 1398, 1291, 1250, 1209, 1180, 1144, 1090, 1034, 961, 916, 856, 824, 778; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 1.7 Hz, 1H), 7.60 (s, 1H), 6.83 (dd, *J* = 8.5, 1.8 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 1.33(s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 166.1, 160.5, 143.5, 132.6, 114.3, 110.6, 103.2, 55.8, 51.8, 39.9, 27.4. HRMS (ESI): m/z Calcd. for $C_{14}H_{20}NO_4$ $[M+H]^+$: 266.1387; found: 266.1395.

***N*-(2-Iodophenyl)pivalamide (2f)**: [23c] Colourless solid (80%); mp. 70-72 °C; IR (NaCl) ν(cm^{-1}) 3274, 2925, 2859, 1654, 1583, 1503, 1469, 1457, 1437, 1366, 1238, 1221, 1175, 1017, 928, 739, 753; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.81 (s, 1H), 7.77 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.34 (m, 1H), 6.83 (td, *J* = 7.8, 1.5 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 138.6, 138.2, 129.2, 125.7, 121.7, 90.1, 40.1, 27.7. HRMS

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Journal Name

(ESI): m/z Calcd. for $C_{11}H_{15}INO$ $[M+H]^+$: 304.0193; found: 304.0197.

***N*-(Pyridin-2-yl)pivalamide (2g):** [23d] Colourless solid (80%); mp. 68-70 °C; IR (NaCl) ν(cm^{-1}) 3333, 2931, 2872, 1690, 1593, 1578, 1513, 1478, 1457, 1430, 1399, 1367, 1302, 1225, 1149, 1096, 1051, 1026, 992, 922, 778; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.1 Hz, 2H), 8.04 (s, 1H), 7.71 (dd, *J* = 12.1, 5.2 Hz, 1H), 7.03 (dd, *J* = 6.9, 5.4 Hz, 1H), 1.33 (s, 9H). HRMS (ESI): m/z Calcd. for $C_{10}H_{15}N_2O$ $[M+H]^+$: 179.1179; found: 179.1179.

***N*-(5-Bromopyridin-2-yl)pivalamide (2h):** [23e] Colourless solid (75%); mp. 61-63 °C; IR (NaCl) ν(cm^{-1}) 3437, 2964, 2931, 2871, 1693, 1584, 1567, 1503, 1398, 1369, 1295, 1224, 1154, 1127, 1093, 1019, 1002, 925, 834, 743, 666; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.17 (s, 1H), 7.79 (t, *J* = 7.3 Hz, 1H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 150.3, 148.4, 140.8, 115.2, 114.4, 39.8, 27.4. HRMS (ESI): m/z Calcd. for $C_{10}H_{14}BrN_2O$ $[M+H]^+$: 257.0284; found: 257.0287.

***N*-(2-Chloropyridin-3-yl)pivalamide (2i):** [23f] Colourless oil (74%); IR (NaCl) ν(cm^{-1}) 3435, 2955, 2923, 2853, 1741, 1594, 1506, 1457, 1385, 1301, 1260, 1205, 1153, 1120, 1073, 1019, 858, 799, 669; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 6.7 Hz, 1H), 8.10 (d, *J* = 8.4 Hz , 1H), 8.01 (s, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 1.36 (s, 9H). HRMS (ESI): m/z Calcd. for $C_{10}H_{14}ClN_2O$ $[M+H]^+$: 213.0789; found: 213.0783.

***N*-(Thiazol-2-yl)pivalamide (2j):** [23g] Colourless solid (80%); mp. 136-138 °C; IR (NaCl) ν(cm^{-1}) 3380, 2922, 2854, 1651, 1598, 1536, 1419, 1402, 1320, 1291, 1247, 1109, 1018, 949, 873; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.45 (d, *J* = 3.6 Hz, 1H), 6.98 (d, *J* = 3.5 Hz, 1H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 159.0, 137.2, 113.7, 39.1, 27.2. HRMS (ESI): m/z Calcd. for $C_8H_{13}N_2OS$ $[M+H]^+$: 185.0743; found: 185.0736.

***N*-Phenylformamide (3a):** [24a] Beige solid (98%); mp. 48-51 °C IR (NaCl) ν(cm^{-1}) 3439, 2955, 2920, 2849, 1730, 1610, 1540, 1439, 1397, 1383, 1276, 1133, 1121, 1089, 953, 879, 773, 678; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.69 (d, *J* = 11.3 Hz, 1H), 8.33 (s, 1H), 8.18 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.32 (m, 4H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 159.9, 137.1, 136.8, 129.7, 129.0, 125.3, 124.8, 120.2, 118.8.

Methyl 4-formamidobenzoate (3b): [11a] Colourless solid (95%); mp. 119-122 °C; IR (NaCl) ν(cm^{-1}) 3264, 2924, 2853, 1714, 1612, 1539, 1436, 1409, 1307, 1282, 1218, 1191, 1177, 1145, 1115, 1016, 846, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.44 (s, 1H), 8.03 (t, *J* = 8.5 Hz, 4H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 3.91 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 166.4, 162.4, 159.6, 141.2, 141.1, 131.5, 130.8, 126.4, 125.9, 119.2, 117.2, 52.2, 52.1.

Methyl 4-formamido-2-methoxybenzoate (3c): Colourless solid (95%); mp. 130-132 °C ; IR (NaCl) ν(cm^{-1}) 3283, 2923, 2852, 1698, 1607, 1595, 1532, 1511, 1453, 1435, 1412, 1326, 1255, 1223, 1188, 1148, 1089, 842, 775; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.64 (s, 1H), 7.55 (s, 1H), 6.87 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 161.9, 159.4, 142.2, 132.8, 115.2, 103.5, 56.0, 51.9; HRMS (ESI): m/z Calcd. for $C_{10}H_{12}NO_4$ $[M+H]^+$: 210.0761; found: 210.0765.

***N*-(2-Hydroxy-5-methylphenyl)formamide (3d):** [24a] Colourless solid (90%); mp. 120-121 °C; IR (NaCl) ν(cm^{-1}) 3435, 2955, 2923, 2852, 1741, 1657, 1596, 1455, 1378, 1243, 1156, 1019, 771, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.66(d, *J* = 8.4 Hz, 1H), 6.75 (s, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 160.6, 147.8, 135.8, 122.0, 121.9, 121.1, 118.0, 20.9.

***N*-(2-Iodophenyl)formamide (3e):** [24b] Colourless solid (90%); mp. 110-112 °C; IR (NaCl) ν(cm^{-1}) 3439, 2955, 2923, 2852, 1739, 1618, 1460, 1383, 1153, 1117, 1019, 773, 669; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.30 (d, *J* = 8.2 Hz, 1H), 7.83 (dd, *J* = 21.4, 8.0 Hz, 1H), 7.45 (s, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 6.91 (dt, *J* = 24.4, 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 157.0, 138.1, 137.2, 127.8, 127.6, 125.2, 124.6, 120.4, 117.3, 88.8, 87.4;

***N*-(Pyridin-3-yl)formamide (3f):** [24c] Colourless solid (86%); mp. 94-96 °C; IR (NaCl) ν(cm^{-1}) 3234, 2922, 2852, 1692, 1588, 1544, 1484, 1426, 1412, 1329, 1286, 1241, 1192, 1154, 1125, 1020, 864, 803, 781; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.47 (s, 2H), 8.25 (d, *J* = 8.1 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.36 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 159.6, 146.4, 140.7, 127.5, 126.1.

***N*-(2-Chloropyridin-3-yl)formamide (3g):** Colourless solid (80%); mp. 145-147 °C ; IR (NaCl) ν(cm^{-1}) 3440, 2927, 2837, 1698, 1599, 1582, 1488, 1429, 1410, 1330, 1290, 1264, 1229, 1212, 1064, 1036, 994, 868, 781, 752, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 8.1 Hz, 1H), 8.56 (s, 1H), 8.13 (d, *J* = 8.8 Hz, 1H), 7.77 (s, 1H), 7.29(m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 159.6, 148.9, 129.7, 121.4, 119.2; HRMS (ESI): m/z Calcd. for $C_6H_6ClN_2O$ $[M+H]^+$: 157.0163; found: 157.0164.

***N*-(5-Bromopyridin-2-yl)formamide (3h):** Colourless solid (78%); mp. 141-143 °C; IR (NaCl) ν(cm^{-1}) 3440, 2922, 2852, 1690, 1593, 1579, 1535, 1463, 1404, 1375, 1306, 1220, 1171, 1094, 1014, 825; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 9.30 (d, *J* = 10.5 Hz, 1H), 8.87 (s, 1H), 8.51 (s, 1H), 8.36 (s, 2H), 8.18 (d, *J* = 8.8 Hz, 1H), 7.84 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.78 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 159.2, 149.5, 149.5, 149.3, 148.5, 141.2, 141.1, 116.1, 115.1, 111.9; HRMS (ESI): m/z Calcd. for $C_6H_6BrN_2O$ $[M+H]^+$: 202.9637; found: 202.9642.

***N*-(Thiazol-2-yl)formamide (3i):** Colourless solid (80%); mp. 159-161 °C; IR (NaCl) ν(cm^{-1}) 3440, 2921, 2852, 1693, 1681, 1597, 1436, 1386, 1352, 1319, 1288, 1169, 1140, 1049, 1018, 854, 834, 748, 726, 672; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.48 (d, *J* = 3.6 Hz, 1H), 7.06 (d, *J* = 3.6 Hz, 1H). ^{13}C NMR (125

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MHz, $CDCl_3$) δ 163.7, 161.7, 142.4, 118.2; HRMS (ESI): m/z Calcd. for $C_4H_5N_2OS$ $[M+H]^+$: 129.0117; found: 129.0123.

***N*-Phenethylformamide (3j):** [11a] Colourless oil (96%); IR (NaCl) ν(cm^{-1}) 3285, 3061, 3029, 2931, 2864, 1666, 1604, 1532, 1497, 1454, 1384, 1237, 1198, 1156, 1085, 1031, 779, 748, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.30 (d, *J* = 5.8 Hz, 2H), 7.22 (dd, *J* = 15.3, 7.7 Hz, 3H), 5.98 (s, 1H), 3.54 (t, *J* = 6.0 Hz, 2H), 2.83 (t, *J* = 5.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 161.6, 138.6, 137.7, 128.9, 128.8, 128.7, 128.6, 126.8, 126.6, 43.3, 39.2, 37.6, 35.4.

Methyl 2-formamido-3-(1*H*-indol-3-yl)propanoate (3k): [24d] Pale yellow solid (85%); mp. 114-117 °C; $[\alpha]^{20}_D$ = + 55 (0.5 $CHCl_3$); IR (NaCl) ν(cm^{-1}) 3346, 2952, 2854, 1739, 1667, 1618, 1512, 1457, 1437, 1382, 1342, 1213, 1180, 1096, 1018, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.13 (s, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 13.1, 5.8 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 1.6 Hz, 1H), 5.01 (dd, *J* = 11.9, 6.5 Hz, 1H), 3.71 (s, 3H), 3.34 (dd, *J* = 5.1, 2.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 161.1, 136.1, 127.5, 123.1, 122.2, 119.6, 118.4, 111.4, 109.3, 52.5, 51.6, 27.5.

Piperidine-1-carbaldehyde (3l): [11a] Colourless oil (87%); IR (NaCl) ν(cm^{-1}) 3298, 2930, 2819, 1720, 1638, 1610, 1538, 1502, 1496, 1428, 1385, 1318, 1257, 1189, 1125, 1083, 1030, 994, 892; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 3.47 (m, 4H), 1.59 (m, 6H).

Morpholine-4-carbaldehyde(3m): [24a] Colourless oil (88%); IR (NaCl) ν(cm^{-1}) 3320, 2920, 2821, 1710, 1640, 1590, 1520, 1472, 1390, 1327, 1254, 1208, 1176, 1109, 1049, 973; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 3.70 (m, 2H), 3.67 (m, 2H), 3.58 (m, 2H), 3.40 (m, 2H).

***N*-(*p*-Tolyl)acetamide (3n):** [24e] Colourless solid (98%); mp. 148-151 °C ; IR (NaCl) ν(cm^{-1}) 3361, 2916, 2849, 1702, 1685, 1610, 1597, 1526, 1443, 1408, 1368, 1314, 1289, 1253, 1175, 1118, 1000, 856, 768; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (br, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 7.5 Hz, 2H), 2.30 (s, 3H), 2.14 (s, 3H).

***N*-(4-Methoxyphenyl)acetamide(3o):** [24e] Colourless solid (97%); mp. 128-129 °C ; IR (NaCl) ν(cm^{-1}) 3242, 2934, 2836, 1647, 1605, 1562, 1513, 1456, 1441, 1369, 1319, 1285, 1246, 1176, 1113, 1030, 970, 838, 773; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (br, 1H), 7.38 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.77 (s, 3H), 2.13 (s, 3H).

***N*-(4-Fluorophenyl)acetamide (3p):** [24f] Colourless solid (95%); mp. 152-154 °C; IR (NaCl) ν(cm^{-1}) 3267, 2923, 1660, 1613, 1565, 1540, 1507, 1400, 1316, 1237, 1208, 1017, 834; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.45 (m, 2H), 6.99 (t, *J* = 8.7 Hz, 2H), 2.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 160.6, 133.9, 121.8, 115.6, 24.3.

***N*-(4-(Trifluoromethoxy)phenyl)acetamide (3q):** Colourless solid (86%); mp. 114-115 °C; IR (NaCl) ν(cm^{-1}) 3435, 2920, 2851, 1672, 1609, 1541, 1512, 1457, 1407, 1377, 1284, 1208, 1162, 1019, 852; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 9.0 Hz, 2H), 7.48 (s, 1H), 7.16 (d, *J* = 8.5 Hz, 2H), 2.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 145.2, 136.5, 128.6, 121.4, 119.4, 24.3; HRMS (ESI): m/z Calcd. for $C_9H_9F_3NO_2$ $[M+H]^+$: 220.0579; found: 220.0582.

***N*-(4-Nitrophenyl)acetamide (3r):** [24f] Colourless solid (85%); mp. 210-212 °C; IR (NaCl) ν(cm^{-1}) 3345, 2921, 2851, 1684, 1617, 1598, 1568, 1507, 1404, 1345, 1304, 1269, 1115, 1018, 849, 750, 668, 513; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.31 (s, 1H), 8.14 (dd, *J* = 9.2, 1.9 Hz, 2H), 7.83 (dd, *J* = 9.2, 2.1 Hz, 2H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, DMSO-*d6*) δ 169.1, 145.0, 142.0, 124.2, 118.4, 24.0.

***N*-(Pyridin-2-yl)acetamide (3s):** [24g] Colourless solid (80%); mp. 70-72 °C; IR (NaCl) ν(cm^{-1}) 3244, 2924,2850, 1690, 1640, 1601, 1584, 1551, 1482, 1424, 1366, 1328, 1288, 1244, 1195, 1133, 1108, 1036, 1020, 918, 855, 838, 818, 706; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.58 (d, *J* = 2.3 Hz, 1H), 8.31 (d, *J* = 3.8 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 7.27 (dd, *J* = 8.2, 4.9 Hz, 1H), 2.20 (s, 3H).

***N*-(4-Bromopyridin-2-yl)acetamide (3t):** Colourless solid (75%); mp. 122-123 °C; IR (NaCl) ν(cm^{-1}) 3241, 2923, 2852, 1681, 1588, 1574, 1540, 1456, 1378, 1304, 1093, 1018, 973, 830, 764; ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.51 (s, 1H), 8.34 (d, *J* = 2.2 Hz, 1H), 8.20 (d, *J* = 8.9 Hz, 1H), 7.94 (d, *J* = 2.5 Hz, 1H), 2.20(s, 3H). ^{13}C NMR (125 MHz, acetone-*d*$_6$) δ 172.5, 170.9, 149.7, 149.3, 141.2, 115.8, 21.5.; HRMS (ESI): m/z Calcd. for $C_7H_8BrN_2O$ $[M+H]^+$: 216.9799; found: 216.9798.

***N*-(Pyridin-3-yl)acetamide (3u):** [24h] Colourless solid (78%); mp. 129-131 °C; IR (NaCl) ν(cm^{-1}) 3256, 2955, 2924, 2853, 1682, 1597, 1578, 1531, 1463, 1434, 1372, 1302, 1239, 1150, 1082, 1017, 965, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.26 (m, 2H), 7.73 (m, 1H), 7.05 (m, 1H), 2.21 (s, 3H).

***N*-(2-(Diethylamino)ethyl)-4-nitrobenzamide (6):** [25] Transamide product **6** was prepared by following general procedure. Viscous yellow oil; (82%); IR (NaCl) ν(cm^{-1}) 3416, 2970, 2929, 1658, 1650, 1600, 1556, 1537, 1488, 1470, 1381, 1346, 1301, 1262, 1177, 1087, 1067, 1014, 870; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.5 Hz, 2H), 8.01 (d, *J* = 8.6 Hz, 2H), 3.62 (dd, *J* = 10.4, 5.0 Hz, 2H), 2.84 (t, *J* = 5.5 Hz, 2H), 2.74 (q, *J* = 7.1 Hz, 4H), 1.13 (t, *J* = 7.1 Hz, 6H); HRMS (ESI): m/z Calcd. for $C_{13}H_{20}N_3O_3$ $[M+H]^+$: 266.1499; found: 266.1501.

Procainamide (7): [25] To a suspension of **6** (1.88 mmol) in ethanol (10 mL) was added reduced iron powder (3.77 mmol). The resulting suspension was reflux for 2h with TLC analysis monitoring for completion of the reaction. The reaction mixture was filtered through celite to remove the iron residue which was washed with ethyl acetate (3x10 mL). The filtrate was partitioned with (2M) KOH solution and the basic layer was further extracted

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Journal Name

with ethyl acetate (3 x 25 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was then subjected to flash silica gel column chromatography to obtain the pure desired product. Orange oil (95%); IR (NaCl) ν(cm^{-1}) 3443, 2917, 2849,1679, 1633, 1587, 1509, 1497, 1467, 1390, 1327, 1298, 1189, 1109, 1074, 949, 847; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.38 (s, 1H), 7.70 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 8.5 Hz, 2H), 3.82 (d, J = 4.6 Hz, 2H), 3.50 (dd, J = 9.3, 4.5 Hz, 2H), 3.44 (m, 4H), 1.40 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, acetone-d_6) δ 171.3, 153.6, 130.2, 120.7, 114.0, 56.0, 49.1, 37.5, 9.5; HRMS (ESI): m/z Calcd. for $C_{13}H_{22}N_3O$ $[M+H]^+$: 236.1758; found: 236.1784.

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Notes and references

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